REMARKS

Claims 44-49, 51-54, 58-61, 63, 64, 66-79, 83 and 84 are pending in the application. Claims 55-57, 62, 65 and 80-82 are cancelled by this Amendment without prejudice.

Claims 44, 52, 63, 79, and 83 have been amended by this Amendment. No new matter is added by the claim amendments. Support is found at least in the Specification at page 4, lines 13-14 and in claims 1-24 as originally filed.

As discussed previously in a telephone call, the applicant's representative would appreciate the opportunity to speak with the Examiner concerning the rejections addressed in this Amendment and Request for Reconsideration. As agreed in that telephone call, the applicant's representative will telephone the week of June 2nd for discussion. In the event that the Examiner receives and reviews this response prior to the week of June 2nd, it is respectfully requested that he contact the undersigned at the telephone number given below prior to the issuance of an Office Action.

Each of the Examiner's rejections or comments is addressed in the order it was presented in Paper No. 12.

I. Restriction Requirement.

At item 2 of Paper No. 12, the Examiner has issued a restriction requirement, contending that: (i) those portions of claims 44, 55-57, 63, and 79 that encompass progenitor cells that are capable of differentiating into other types of neurons than dopaminergic neurons encompasses a distinct invention; and (ii) claim 50 is a different invention because the progenitor cells are derived from umbilical cord blood. Further, the Examiner asserts that since the applicant has received an action on the merits for the original presented invention, he considers that the applicant has provisionally elected prosecution of claims directed to dopaminergic neurons. Accordingly, he has withdrawn all other subject matter from consideration as being directed to non-elected inventions.

With respect to (i) above, while the applicant does not necessarily agree with the Examiner, they have cancelled those portions of the claims which recite non-dopaminergic

neurons, in order to facilitate the prosecution of this invention. The cancellation of the subject matter of the claims related to progenitor cells that are capable of differentiating into substantially only cholinergic, GABAergic, and serotonergic neurons is undertaken without prejudice to the filing of claims directed to such subject matter in subsequent applications which are related to this one under 35 U.S.C. § 120.

II. Objection to Claim 52 - Improper Dependent Form.

At item 4 of Paper No. 12, the Examiner has objected to claim 52, asserting that it is of "improper dependent form for failing to limit the subject matter of the previous claim." The applicant respectfully traverses this rejection. Claim 52 is dependent from claim 44. It therefore incorporates all of the elements of claim 44, as well as those elements recited in claim 52. Thus, claim 52 is not an improper independent claim as it claims a neuronal tissue derived from brain or spinal cord tissue of a mammal, which tissue is derived from a single cell.

Therefore, it is respectfully requested that the Examiner reconsider and withdraw his objection to claim 52.

III. Rejection under 35 U.S.C. § 112, first paragraph - Written Description.

At item 5 of Paper No. 12, the Examiner has rejected claims 44-49, 51-54, and 58-84 under 35 U.S.C. § 112, first paragraph, asserting that these claims are not supported by the written description provided in the specification. The Examiner argues that there is no written support in the Specification for the following phrases recited in the claims:

(i) "synthetic neuronal tissue,"

(ii) "partially differentiated neuronal progenitor cells that maintain their capability to perform mitosis,"

(iii) ". . . differentiation-promoting factor are contacted for at least two hours,"

(iv) "separated . . . after at least two hours,"

(v) "wherein the factor is an extra cellular matrix of human tissue,"

(vi) "wherein the recipient and the mammal are the same individual,"

(vii) "wherein the single progenitor cell is selected on the basis that it expresses a marker characteristic of the selected type of neuron,"

(viii) "the single neuronal progenitor cell is proliferated by contacting the cell with a mitogen after selecting the cell,"

(ix) "wherein the synthetic tissue does not comprise sufficient glial cells to provoke an immune response . . . recipient,"

(x) "<90% [95%] of cells in the synthetic tissue are the progenitor cells,"

(xi) "partial differentiation is performed more than once," and

(xii) "proliferating the sub-cloned partially-differentiated neuronal progenitor cell." The applicant respectfully traverses these rejections for the reasons given below.

None of the subject matters listed above is new matter under § 112, first paragraph. Subject matter is only "new" if it is not supported by a written description in the Specification of the application. The test for sufficiency of support is whether the Specification conveys with reasonable clarity to those skilled in the art that the inventor was in possession of the invention at the time of feeling. M.P.E.P. 2163.02. In making such determinations, it is axiomatic that the disclosure must be considered as a whole. See id. However, since there is in haec verba requirement, it is sufficient that the elements of the claims are supported expressly, implicitly, or inherently. M.P.E.P. 2163.

"Synthetic neuronal tissue" (item i, above) does not describe new matter. As discussed in the prior Office Action, use of this phrase is merely a designation of the claimed composition of matter. This composition of matter is disclosed throughout the specification, for example, at page 1, lines 26-30, and at page 2, lines 15-17. As the disclosure indicates, the tissue can be derived from "natural" neuronal tissue taken from either the brain or the spinal cord of a mammal; therefore, it is synthetic as it has been the subject of human manipulation.

Support for "partially differentiated neuronal progenitor cells that maintain their capability to perform mitosis" (ii, above) is found in the Specification at least at page 3, lines 12-14, 17-19. ("tissue . . . is prepared according to the invention which includes . . . partial differentiation in vitro."; as used in the invention "[a] population of determined neuronal progenitor cells that have been selected and partially differentiated maintains the ability to perform mitosis allowing for performing subsequent proliferation step."). As is clear from review of the specification coupled with the knowledge of a person of skill in the art, partially differentiated cells are those which have descended sufficiently far on the differentiation pathways such that they are no longer totipotent, but have not entered into the phase of terminal differentiation, and as such, remain capable of differentiating into different "species" of neuronal tissues, such as dopaminergic neurons. See also pages 5-7 of the Specification (describing partial differentiation of neuronal progenitor cells that maintain their ability to mitose).

Claims 80 and 81 have been cancelled; therefore, the Examiner's rejection with respect to (iii) and (iv) above is no longer applicable.

Claims 62 and 65 have been cancelled; therefore, the Examiner's rejection with respect to (v), above, is no longer applicable.

Claim 82 has been cancelled; thus, the Examiner's rejection with respect to (vi), above, is inapplicable.

Claim 83 has been amended and no longer contains the language to which the Examiner directed his rejection (vii). Therefore, the rejection on this basis is considered to be no longer applicable.

The Examiner states the Specification lacks written description support for "the single neuronal progenitor cell is proliferated by contacting the cell with a mitogen after selecting the cell" (viii, above). To the contrary, support for this language is found in the Specification at least at page 9, lines 23-34, to page 10, lines 1-25.

The Examiner argues that those portions of the claims reciting "wherein the synthetic tissue does not comprise sufficient glial cells to provoke an immune response . . . recipient" (ix,

above) is not supported in the Specification. To the contrary, the applicant directs the Examiner's attention to page 2, lines 3-12:

> This invention is based on the concept that neuronal progenitor (precursor) cells can be isolated and expanded in vitro. . . . Using this treatment, one can generate tissue cultures that almost substantially contain immediate precursors of specific neurons. <u>These cultures do not include cells that give rise to immunogeneic glial cells in large enough quantities to induce any detectable immune response.</u>

(emphasis added.)

Thus, while the synthetic tissues of the claimed invention may contain a certain amount of glial cells, it is defined in the claim that such amount cannot be sufficient such that an immune reaction is provoked. The Examiner seems to believe that since the applicant has not specified a quantity of glial cells, that such claim is indefinite. This is neither a correct statement of law nor does it reflect an understanding of the knowledge of a person of skill in the art, the requisite standard by which a § 112 determination must be made. To a person of skill in the art, it is easily and routinely determined the number of glial cells which will induce an immune response, and is considered in the ordinary course of events to be variable depending on several factors, including the species of mammal to which the tissue is transplanted.

As discussed in the prior response, whether or not a material such as a glial cell will evoke an immune response within a given species or even an individual, depends on, inter alia, the dosage of the material to which the animal is subjected. The invention which is described definitely in the claims is a synthetic neuronal tissue composition, and methods of making such tissues, which contain so few glial cells that the presence of the glial cells does not reach the immunogenic threshold of the organism into which the tissue is implanted. Therefore, it does not trigger an immune response upon implantation into a recipient. Under the § 112, the applicant is not required to specify a quantity of glial cells that the claimed tissue does or does not possess; it is sufficient that this characteristic is recited in the claims, and that a person of ordinary skill could easily determine which synthetic neuronal tissues fall within the scope of the claim and which do not, based upon the provocation, or absence of provocation, of an immune response.

The Examiner also considers unclear the terminology "less than 90% [95%] of the cells in the synthetic tissue are the progenitor cells." (item x, above) As pointed out in a prior response, there is express support for this claim element in the Specification. See, the Specification at least at page 2, lines 17-18 ("the percentage of such specific neurons in the tissue samples should be greater than 90%, preferably greater 95%"). "Greater than" is the same as "more than." Thus, the Examiner's rejection on this ground is unfounded. Further, it is well known in the art that a "tissue" is comprised of cells; if the Examiner is suggesting that there is no antecedent basis for "cells in the synthetic tissue" in claim 44, this is incorrect.

Finally, the Examiner rejects the claims based upon the lack of written description for the language "partial differentiation is performed more than once" and "proliferating the sub-cloned partially-differentiated neuronal progenitor cell." Support for each of these phrases is provided expressly in the Specification. The "partial differentiation" language is supported in the Specification at least at page 5, lines 2-16. ("Priming includes intermittent treatment of neuronal progenitor cells with one or more compounds that promote differentiation in specific neurons. . . . Priming may be repeated several times using identical or alternative combinations and/or concentrations of differentiation promoting compounds.")

For at least these reasons, it is respectfully requested that the Examiner reconsider and withdraw the 35 U.S.C. § 112, first paragraph, rejections.

IV. Rejection Under 35 U.S.C. § 112, Second Paragraph - Definiteness.

The Examiner has rejected claims 44-49, 51-54, and 58-84 under 35 U.S.C. § 112, second paragraph, asserting that these claims are indefinite for a failure to particularly point out and distinctly claim the subject matter to which they are directed. Specifically, the Examiner states that the claims are rejected for reasons made of record for cancelled claims 26-43, i.e., the reasons set forth in numbered paragraph 5 (page 4) in the Examiner's Office Action mailed April 9, 2002 (Paper No. 9), and the additional comments provided in this Office Action. The applicant respectfully traverses this rejection.

The applicant first addresses the Examiner's rejection as it relates to the language set forth in numbered paragraph 5 of Paper No. 9. In Paper No. 9 the Examiner argued that the phrase "not containing any physiologically active amounts of amino competent glial cells" was

indefinite. None of the new claims contains this language; therefore the Examiner's rejection on this basis is inapplicable. The Examiner also considered "tissue material and differentiating-promoting factor" or "exogenous factors" to be "unknown and ambiguous" and therefore indefinite. The term "exogenous factor" is not used in any of the presently pending claims. Further, the term "differentiation-promoting factor" is not indefinite, as a person of skill in the art upon review of the Specification would understand this term to encompass those factors which, when contacted with the neural progenitor cells, promote the proliferation and differentiation of such cells. The process of differentiation is well known in the art as a process whereby relatively unspecialized cells, in this case neural progenitor cells, acquire specialized structural and/or functional features that characterize the determined cell tissues or organs.

With respect to the term "issue according to claim 26," such phrase is no longer present in any of the pending claims. Therefore, it is considered that the Examiner's rejection is inapplicable.

With respect to the terminology set forth in Paper No. 12, which the Examiner asserts is indefinite, the applicant responds as follows. With respect to the term "synthetic neuronal tissue," as specified above, synthetic neuronal tissue refers to the composition of matter described throughout this application, namely neuronal tissue derived from "natural" neuronal tissue taken from either the brain or the spinal cord of a mammal; it is synthetic as it has been the subject of human manipulation.

The phrase "factor . . . [can be] an extra cellular matrix of human tissue" is no longer present in the pending claims. Therefore, the Examiner's rejection on this ground is no longer applicable.

The Examiner also seems to be maintaining his rejection of the claim language describing the quantity of glial cells present in the synthetic tissue, specifically the language "wherein the synthetic tissue does not comprise sufficient glial cells to provoke an immune response upon implantation of the synthetic tissue into a recipient." The Examiner's position seems to be that a "synthetic tissue" is either rejected by the host or it is not. As is known to a person of skill in the art, such statement is an oversimplification of the processes of the immune system. This language is neither unnecessary nor confusing as its recitation in claims defines a specific

structural aspect of the synthetic tissue, i.e., it does not contain sufficient glial cells to provoke an immune response when implanted into the selected mammalian patient. As discussed above, whether or not a material such as a glial cell will evoke an immune response within a given species or even a given individual depends on, inter alia, the dosage of the material (the amount of glial cells present) to which the animal is subjected. Thus, the recitation in the claims is not directed to the rejection or acceptance of the synthetic tissue by the mammal into which the tissue is implanted, but rather is a measure of the number of glial cells present in the tissue. For example, there may be a situation where there is a sufficient amount of glial cells to provoke an immune response, but the tissue is not rejected by the mammal into which it is implanted.

In view of the foregoing, it is respectfully submitted that the applicant has overcome the Examiner's rejections relating to 35 U.S.C. § 112, first paragraph. Accordingly, it is requested that the Examiner reconsider and withdraw the rejection.

V. Rejection Under 35 U.S.C. § 102(b) Based Upon U.S. Patent No. 5,411,883.

At item 7 of Paper No. 12, the Examiner has maintained his rejection of claims 44-49, 51-54, and 58-84 under 35 U.S.C. § 102(b) as being anticipated by U.S. Patent No. 5,411,883 of Boss, et al. (Boss). As basis for this rejection, the Examiner contends that Boss teaches isolation of human and porcine neuron progenitor cells that are "brain derived neuronal tissue" from the mesencephalon. According to the Examiner, these cells inherently contain progeny of a single totipotent neural stem cell derived from immitor progenitor cells. The Examiner states that Boss describes dissection, isolation of progenitor cells and proliferation of progenitor cells. Additionally, the Examiner believes that Boss describes partial differentiation, full differentiation, and selection of individual cells expressing dopaminergic markers. The Examiner asserts that the Boss tissues inherently possess the characteristic of "not containing any physiologically active amounts of immuno-competent glial cells, because no graft rejection/immuno-response was observed or mentioned by Boss. The applicant respectfully traverses this rejection.

Boss is directed to isolation and culture methods designed to proliferate neuron progenitor cells in vitro to produce a culture which differentiates to produce dopamine-producing cells. The cells of the Boss invention either spontaneously differentiate in vitro, or can be

induced to differentiate in vitro, producing a population of mature neurons which produce dopamine, prior to implantation into the host. Column 3, lines 58-60. The neuron progenitor cells of the Boss invention are derived from the mesencephalon tissue obtained from a mammalian donor (from the dopaminergic system of the brain). The Boss cultures are described as being two dimensional monolayers in which differentiating neurons and glial cells can be observed. Column 6, lines 10-12. It is these cultures, which are already differentiated into neurons and glial cells, that are implanted into the host. See id.; see column 13, lines 65-67 ("Following completion of differentiation, differentiated progenitor cells in the culture cease proliferation and are preferably transplanted.") Thus, the tissue culture of the Boss invention to be implanted in a host comprises fully differentiated neuronal progenitor cells, which are incapable of undergoing mitosis.

In order to anticipate an invention under 35 U.S.C. § 102(b), the disclosed reference must teach each element of the invention as claimed. Boss does not meet this threshold burden. Boss does not teach a synthetic neuronal tissue comprising partially differentiated neural progenitor cells. The tissue culture in Boss is fully terminally differentiated prior to implantation and therefore the tissue of Boss is not the same as the inventive synthetic tissue. Further, Boss does not teach a synthetic neuronal tissue that comprises cells which maintain the ability to undergo mitosis. The cells which make up the tissue culture of Boss are, by virtue of their terminal differentiation, no longer able to engage in the mitotic processes required for cell division. In contrast, the synthetic neuronal tissue of the invention includes cells that are partially-differentiated neuronal progenitor cells that maintain the capacity to perform mitosis.

Finally, there is no teaching, either expressly or inherently, that the tissue culture of Boss does not contain sufficient glial cells to provoke an immune response upon implantation of the synthetic tissue into the recipient. The Examiner argues that this characteristic is inherently present in the Boss disclosure, merely because Boss does not discuss, one way or the other, whether the implanted tissue cultures invoked an immune response. The Examiner's reasoning is legally and technically flawed. The mere absence of a disclosure of an element in a reference, does not allow the Examiner to make the inference that the element is present, unless the Examiner has provided a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of

the applied prior art. In the present case, the Examiner has provided no such basis, and has instead improperly relied upon unsupported assertions of the allegedly inherent properties of the cell preparation of Boss, based upon an absence of information in the reference.

Accordingly, because the Boss reference does not teach at least these elements recited in the claims of the present invention, Boss does not anticipate the invention under 35 U.S.C. § 102(b). It is respectfully requested that the Examiner reconsider and withdraw the rejection.

VI. Rejection under 35 U.S.C. § 102(b) based upon Luskin.

At item 8, of Paper No. 12, the Examiner has rejected claims 44-49, 51-54 and 58-84 under 35 U.S.C. § 102(b) as being anticipated by International Patent Application Publication WO 97/02049 of Luskin. As basis for the rejection, the Examiner states that Luskin teaches isolation of human and mammalian brain-derived neuronal progenitor cells capable of differentiating into more than 90% dopaminergic neurons. According to the Examiner, Luskin's progenitor cells contain less than 5%, and even less than 2% glial cells. The Examiner states that "immature progenitor cells" are inherently the progeny of single multi-potent neural stem cells. The Examiner further states that Luskin describes partial differentiation, full differentiation, and selection of individual cells expressing dopaminergic markers. The applicant respectfully traverses the rejection.

Luskin discloses that the neuronal progenitor cells in the Luskin composition express a neuron-specific marker. However, these progenitor cells can differentiate to become any of a variety of types of neuron cells. For example, in the abstract, Luskin discloses that the neuronal progenitor cells can give rise to progeny cells which are able to differentiate into various types of neuronal cells. Thus, the cells are not sufficiently differentiated that they are capable of becoming only one type of neuronal cell, as are the cells that comprise the synthetic neuronal tissue of the claimed invention.

In contrast, the claims of the invention recite that the neural progenitor cells that comprise the synthetic neuronic tissue of the invention are able to differentiate substantially into only a single type of neuron, a dopaminergic neuron. For at least this reason, the disclosures of Luskin do not anticipate the invention as claimed.

Accordingly, it is respectfully requested that the Examiner reconsider and withdraw the rejection of claims 44-49, 51-54, and 58-84.

CONCLUSION

In view of the foregoing, it is respectfully submitted that the applicant has demonstrated each of the claims of the invention to be patentably distinct over the art of record and are fully compliant with 35 U.S.C. § 112. Accordingly, it is respectfully requested that the Examiner reconsider and withdraw the rejections. Allowance of claims 44-49, 51-54, 58-61, 63, 64, 66-79, 83 and 84 at the earliest opportunity is respectfully solicited.

Respectfully submitted,

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